Genetic fine-mapping of the Iowan SNCA gene triplication in a patient with Parkinson's disease.

Journal: NPJ Parkinsons Dis

Publication Year: 2018

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PubMed link: 29928688

Funding Grants: San Jose State University Stem Cell Internships for Laboratory-based Learning (SJSU SCILL)

Public Summary:
The "Iowa kindred," a large Iowan family with autosomal dominant Parkinson's disease, has been followed clinically since the 1920s at the Mayo Clinic. In 2003, the genetic cause was determined to be a 1.7 Mb triplication of the alpha-synuclein genomic locus. Affected individuals present with an early-onset, severe parkinsonism-dementia syndrome. Here, we present a descendant of the Iowa kindred with novel, disease-associated non-motor findings of reduced heart rate variability, complete anosmia, and a rare skin condition called colloid milium. At autopsy, key neuropathological findings were compatible with diffuse Lewy body disease. Using high-resolution comparative genomic hybridization (CGH) array analysis to fine-map the genomic breakpoints, we observed two independent recombination events of the SNCA locus that resulted in a genomic triplication of twelve genes, including SNCA, and the disruption of two genes, HERC6 and CCSER1, at the genomic breakpoints. In conclusion, we provide further evidence that the mere two-fold overexpression of alpha-synuclein leads to a fulminant alpha-synucleinopathy with rapid progression and severe clinical and neuropathological features.

Scientific Abstract:
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